

CLAIMS

What is claimed is:

1. ~~A method to diagnose a subject prior to the onset of Alzheimer's disease, the method comprising~~
 - ~~—— (a) providing an isolated tau sample obtained from the subject and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
 - ~~—— (b) diagnosing the subject as having an increased risk for conversion to mild cognitive impairment due to Alzheimer's disease when tau phosphorylation at T217 or T181 is about 1.5σ or above and tau phosphorylation at T205 is about 1.5σ or below, where σ is the standard deviation defined by the normal distribution of tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.~~
2. ~~The method of claim 1, wherein the subject is diagnosed when tau phosphorylation at T217 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .~~
3. ~~The method of claim 2, wherein the subject is diagnosed when (i) tau phosphorylation at T217 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T217 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T217 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .~~
4. ~~The method of claim 2, wherein the subject is diagnosed when tau phosphorylation at T217 is above 2σ and tau phosphorylation at T205 is below 2σ .~~
5. ~~The method of claim 1, wherein the subject is diagnosed when tau phosphorylation at T181 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .~~

- ~~6. The method of claim 5, wherein the subject is diagnosed when (i) tau phosphorylation at T181 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T181 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T181 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .~~
- ~~7. The method of claim 5, wherein the subject is diagnosed when tau phosphorylation at T181 is above 2σ and tau phosphorylation at T205 is below 2σ .~~
- ~~8. The method of claim 1, wherein the subject is diagnosed when tau phosphorylation at T181 and T217 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .~~
- ~~9. The method of claim 8, wherein the subject is diagnosed when (i) tau phosphorylation at T181 and T217 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T181 and T217 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T181 and T217 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .~~
- ~~10. The method of claim 8, wherein the subject is diagnosed when tau phosphorylation at T181 and T217 is above 2σ and tau phosphorylation at T205 is below 2σ .~~
- ~~11. A method of any one of claims 1 to 10, wherein the diagnosis further includes an identification of the subject as about 10 to about 25 years from the onset of mild cognitive impairment due to Alzheimer's disease.~~
- ~~12. The method of claim 11, wherein the diagnosis further includes an identification of the subject as about 10 to about 20 years from the onset of mild cognitive impairment due to Alzheimer's disease.~~
- ~~13. A method to diagnose a subject prior to the onset of Alzheimer's disease, the method comprising~~

~~—— (a) providing an isolated tau sample obtained from the subject and measuring total tau and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~

~~—— (b) diagnosing the subject as having an increased risk for conversion to mild cognitive impairment due to Alzheimer's disease when the ratio of tau phosphorylation at T217 or T181 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is below 2σ , where σ is the standard deviation defined by the normal distribution of total tau and tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.~~

~~14. The method of claim 13, wherein the subject is diagnosed when the ratio of tau phosphorylation at T217 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5σ .~~

~~15. The method of claim 14, wherein the subject is diagnosed when (i) the ratio of tau phosphorylation at T217 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75σ , (ii) the ratio of tau phosphorylation at T217 to total tau T217 is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau T205 is below 1.8σ , or (iii) the ratio of tau phosphorylation at T217 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9σ .~~

~~16. The method of claim 14, wherein the subject is diagnosed when the ratio of tau phosphorylation at T217 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is below 2σ .~~

~~17. The method of claim 13, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5σ .~~

- ~~18. The method of claim 17, wherein the subject is diagnosed when (i) the ratio of tau phosphorylation at T181 to total tau is above 1.75 σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75 σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8 σ and the ratio of tau phosphorylation at T205 to total tau is below 1.8 σ , or (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9 σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9 σ .~~
- ~~19. The method of claim 17, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau is above 2 σ and the ratio of tau phosphorylation at T205 to total tau is below 2 σ .~~
- ~~20. The method of claim 13, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.5 σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5 σ .~~
- ~~21. The method of claim 20, wherein the subject is diagnosed when (i) the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.75 σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75 σ , (ii) the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.8 σ and the ratio of tau phosphorylation at T205 to total tau is below 1.8 σ , or (iii) the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.9 σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9 σ .~~
- ~~22. The method of claim 20, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 2 σ and tau phosphorylation at T205 is below 2 σ .~~

23. ~~A method of any one of claims 13 to 22, wherein the diagnosis further includes an identification of the subject as about 10 to about 25 years from the onset of mild cognitive impairment due to Alzheimer's disease.~~
24. ~~The method of claim 23, wherein the diagnosis further includes an identification of the subject as about 10 to about 20 years from the onset of mild cognitive impairment due to Alzheimer's disease.~~
25. ~~A method to diagnose a subject prior to the onset of Alzheimer's disease, the method comprising~~
~~—— (a) providing an isolated tau sample obtained from the subject and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
~~—— (b) diagnosing the subject as having an increased risk for conversion to mild cognitive impairment due to Alzheimer's disease when tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217 is about 1.5σ or above, where σ is the standard deviation defined by the normal distribution of tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.~~
26. ~~The method of claim 24, wherein the subject is diagnosed when tau phosphorylation at T217 and T205 is above 1.5σ .~~
27. ~~The method of claim 26, wherein the subject is diagnosed when tau phosphorylation at T217 and T205 is above 1.75σ , is above 1.8σ , or is above 1.9σ .~~
28. ~~The method of claim 26, wherein the subject is diagnosed when tau phosphorylation at T217 and T205 is above 2σ .~~
29. ~~The method of claim 25, wherein the subject is diagnosed when tau phosphorylation at T181 and T205 is above 1.5σ .~~

- ~~30. The method of claim 29, wherein the subject is diagnosed when tau phosphorylation at T181 and T205 is above 1.75 σ , is above 1.8 σ , or is above 1.9 σ .~~
- ~~31. The method of claim 29, wherein the subject is diagnosed when tau phosphorylation at T181 and T205 is above 2 σ .~~
- ~~32. The method of claim 25, wherein the subject is diagnosed when tau phosphorylation at T181, T205, and T217 is above 1.5 σ .~~
- ~~33. The method of claim 32, wherein the subject is diagnosed when tau phosphorylation at T181, T205, and T217 is above 1.75 σ , is above 1.8 σ , or is above 1.9 σ .~~
- ~~34. The method of claim 32, wherein the subject is diagnosed when tau phosphorylation at T181, T205, and T217 is above 2 σ .~~
- ~~35. A method of any one of claims 25 to 34, wherein the diagnosis further includes an identification of the subject as about 15 years or less from the onset of mild cognitive impairment due to Alzheimer's disease.~~
- ~~36. The method of claim 35, wherein the diagnosis further includes an identification of the subject as about 10 years or less from the onset of mild cognitive impairment due to Alzheimer's disease.~~
- ~~37. A method to diagnose a subject prior to the onset of Alzheimer's disease, the method comprising~~
~~—— (a) providing an isolated tau sample obtained from the subject and measuring total tau and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
~~—— (b) diagnosing the subject as having an increased risk for conversion to mild cognitive impairment due to Alzheimer's disease when the ratio of tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217 to total tau is about 1.5 σ or above, where σ is the standard deviation~~

defined by the normal distribution of total tau and tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.

38. The method of claim 37, wherein the subject is diagnosed when the ratio of tau phosphorylation at T217 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is above 1.5σ .
39. The method of claim 38, wherein the subject is diagnosed when (i) the ratio of tau phosphorylation at T217 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is above 1.75σ , (ii) the ratio of tau phosphorylation at T217 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is above 1.8σ , (iii) the ratio of tau phosphorylation at T217 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is above 1.9σ .
40. The method of claim 38, wherein the subject is diagnosed when the ratio of tau phosphorylation at T217 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is above 2σ .
41. The method of claim 37, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is above 1.5σ .
42. The method of claim 41, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is above 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is above 1.8σ , (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is above 1.9σ .

43. The method of claim 41, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is above 2σ .
44. The method of claim 37, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ , the ratio of tau phosphorylation at T205 to total tau is above 1.5σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.5σ .
45. The method of claim 44, wherein the subject is diagnosed when (i) the ratio of tau phosphorylation at T181 to total tau is above 1.75σ , the ratio of tau phosphorylation at T205 to total tau is above 1.75σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8σ , the ratio of tau phosphorylation at T205 to total tau is above 1.8σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.8σ , (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9σ , the ratio of tau phosphorylation at T205 to total tau is above 1.9σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.9σ .
46. The method of claim 44, wherein the subject is diagnosed when the ratio of tau phosphorylation at T181 to total tau is above 2σ , the ratio of tau phosphorylation at T205 to total tau is above 2σ , and the ratio of tau phosphorylation at T217 to total tau is above 2σ .
47. A method of any one of claims 37 to 46, wherein the diagnosis further includes an identification of the subject as about 15 years or less from the onset of mild cognitive impairment due to Alzheimer's disease.
48. The method of claim 47, wherein the diagnosis further includes an identification of the subject as about 10 years or less from the onset of mild cognitive impairment due to Alzheimer's disease.
49. A method for treating a subject in need thereof, the method comprising

—— (a) providing an isolated tau sample obtained from the subject and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and

—— (b) administering a pharmaceutical composition to the subject when tau phosphorylation at T217 or T181 is about 1.5σ or above and tau phosphorylation at T205 is about 1.5σ or below, where σ is the standard deviation defined by the normal distribution of tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.

50. The method of claim 48, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T217 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .

51. The method of claim 50, wherein the subject is administered a pharmaceutical composition when (i) tau phosphorylation at T217 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T217 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T217 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .

52. The method of claim 50, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T217 is above 2σ and tau phosphorylation at T205 is below 2σ .

53. The method of claim 49, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .

54. The method of claim 53, wherein the subject is administered a pharmaceutical composition when (i) tau phosphorylation at T181 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T181 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T181 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .

55. ~~The method of claim 53, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181 is above 2σ and tau phosphorylation at T205 is below 2σ .~~
56. ~~The method of claim 49, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181 and T217 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .~~
57. ~~The method of claim 56, wherein the subject is administered a pharmaceutical composition when (i) tau phosphorylation at T181 and T217 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T181 and T217 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T181 and T217 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .~~
58. ~~The method of claim 56, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181 and T217 is above 2σ and tau phosphorylation at T205 is below 2σ .~~
59. ~~A method for treating a subject in need thereof, the method comprising~~
~~—— (a) providing an isolated tau sample obtained from the subject and measuring total tau and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
~~—— (b) administering a pharmaceutical composition to the subject when the ratio of tau phosphorylation at T217 or T181 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is below 2σ , where σ is the standard deviation defined by the normal distribution of total tau and tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.~~

60. The method of claim 59, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T217 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5σ .
61. The method of claim 60, wherein the subject is administered a pharmaceutical composition when (i) the ratio of tau phosphorylation at T217 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75σ , (ii) the ratio of tau phosphorylation at T217 to total tau T217 is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau T205 is below 1.8σ , or (iii) the ratio of tau phosphorylation at T217 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9σ .
62. The method of claim 60, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T217 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is below 2σ .
63. The method of claim 59, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5σ .
64. The method of claim 63, wherein the subject is administered a pharmaceutical composition when (i) the ratio of tau phosphorylation at T181 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is below 1.8σ , or (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9σ .
65. The method of claim 63, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is below 2σ .
66. The method of claim 59, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau and the

~~ratio of tau phosphorylation at T217 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5σ .~~

~~67. The method of claim 66, wherein the subject is administered a pharmaceutical composition when (i) the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is below 1.8σ , or (iii) the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9σ .~~

~~68. The method of claim 66, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 2σ and tau phosphorylation at T205 is below 2σ .~~

~~69. A method for treating a subject in need thereof, the method comprising~~
~~—— (a) providing an isolated tau sample obtained from the subject and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
~~—— (b) administering a pharmaceutical composition to the subject when tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217 is about 1.5σ or above, where σ is the standard deviation defined by the normal distribution of tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.~~

~~70. The method of claim 69, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T217 and T205 is above 1.5σ .~~

- ~~71. The method of claim 70, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T217 and T205 is above 1.75σ , is above 1.8σ , or is above 1.9σ .~~
- ~~72. The method of claim 70, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T217 and T205 is above 2σ .~~
- ~~73. The method of claim 69, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181 and T205 is above 1.5σ .~~
- ~~74. The method of claim 73, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181 and T205 is above 1.75σ , is above 1.8σ , or is above 1.9σ .~~
- ~~75. The method of claim 73, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181 and T205 is above 2σ .~~
- ~~76. The method of claim 69, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181, T205, and T217 is above 1.5σ .~~
- ~~77. The method of claim 76, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181, T205, and T217 is above 1.75σ , is above 1.8σ , or is above 1.9σ .~~
- ~~78. The method of claim 76, wherein the subject is administered a pharmaceutical composition when tau phosphorylation at T181, T205, and T217 is above 2σ .~~
- ~~79. A method for treating a subject in need thereof, the method comprising~~
~~—— (a) providing an isolated tau sample obtained from the subject and measuring total tau and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
~~—— (b) administering a pharmaceutical composition to the subject when the ratio of tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217 to total tau is about 1.5σ or above, where σ is the standard deviation defined by the normal distribution of total tau and tau phosphorylation~~

at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.

80. The method of claim 79, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T217 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is above 1.5σ .

81. The method of claim 80, wherein the subject is administered a pharmaceutical composition when (i) the ratio of tau phosphorylation at T217 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is above 1.75σ , (ii) the ratio of tau phosphorylation at T217 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is above 1.8σ , (iii) the ratio of tau phosphorylation at T217 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is above 1.9σ .

82. The method of claim 80, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T217 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is above 2σ .

83. The method of claim 79, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is above 1.5σ .

84. The method of claim 83, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is above 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is above 1.8σ , (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is above 1.9σ .

85. ~~The method of claim 83, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is above 2σ .~~
86. ~~The method of claim 79, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ , the ratio of tau phosphorylation at T205 to total tau is above 1.5σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.5σ .~~
87. ~~The method of claim 86, wherein the subject is administered a pharmaceutical composition when (i) the ratio of tau phosphorylation at T181 to total tau is above 1.75σ , the ratio of tau phosphorylation at T205 to total tau is above 1.75σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8σ , the ratio of tau phosphorylation at T205 to total tau is above 1.8σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.8σ , (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9σ , the ratio of tau phosphorylation at T205 to total tau is above 1.9σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.9σ .~~
88. ~~The method of claim 86, wherein the subject is administered a pharmaceutical composition when the ratio of tau phosphorylation at T181 to total tau is above 2σ , the ratio of tau phosphorylation at T205 to total tau is above 2σ , and the ratio of tau phosphorylation at T217 to total tau is above 2σ .~~
89. ~~A method for enrolling a subject in a clinical trial, the method comprising~~
~~—— (a) providing an isolated tau sample obtained from the subject and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
~~—— (b) enrolling the subject in a clinical trial when tau phosphorylation at T217 or T181 is about 1.5σ or above and tau phosphorylation at T205 is about 1.5σ or below, where σ is the standard deviation defined by the normal distribution of tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217~~

measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.

90. The method of claim 89, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T217 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .
91. The method of claim 90, wherein the subject is enrolled in the clinical trial when (i) tau phosphorylation at T217 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T217 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T217 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .
92. The method of claim 90, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T217 is above 2σ and tau phosphorylation at T205 is below 2σ .
93. The method of claim 89, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .
94. The method of claim 93, wherein the subject is enrolled in the clinical trial when (i) tau phosphorylation at T181 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T181 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T181 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .
95. The method of claim 93, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181 is above 2σ and tau phosphorylation at T205 is below 2σ .
96. The method of claim 89, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181 and T217 is above 1.5σ and tau phosphorylation at T205 is below 1.5σ .

- ~~97. The method of claim 96, wherein the subject is enrolled in the clinical trial when (i) tau phosphorylation at T181 and T217 is above 1.75σ and tau phosphorylation at T205 is below 1.75σ , (ii) tau phosphorylation at T181 and T217 is above 1.8σ and tau phosphorylation at T205 is below 1.8σ , or (iii) tau phosphorylation at T181 and T217 is above 1.9σ and tau phosphorylation at T205 is below 1.9σ .~~
- ~~98. The method of claim 96, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181 and T217 is above 2σ and tau phosphorylation at T205 is below 2σ .~~
- ~~99. A method for enrolling a subject in a clinical trial, the method comprising~~
~~—— (a) providing an isolated tau sample obtained from the subject and measuring total tau and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
~~—— (b) enrolling the subject in a clinical trial when the ratio of tau phosphorylation at T217 or T181 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is below 2σ , where σ is the standard deviation defined by the normal distribution of total tau and tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.~~
- ~~100. — The method of claim 99, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T217 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5σ .~~
- ~~101. — The method of claim 100, wherein the subject is enrolled in the clinical trial when (i) the ratio of tau phosphorylation at T217 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75σ , (ii) the ratio of tau phosphorylation at T217 to total tau T217 is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau T205 is below 1.8σ , or (iii) the ratio of tau phosphorylation at T217 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9σ .~~

- ~~102. — The method of claim 100, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T217 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is below 2σ .~~
- ~~103. — The method of claim 99, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5σ .~~
- ~~104. — The method of claim 103, wherein the subject is enrolled in the clinical trial when (i) the ratio of tau phosphorylation at T181 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is below 1.8σ , or (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9σ .~~
- ~~105. — The method of claim 103, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is below 2σ .~~
- ~~106. — The method of claim 99, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is below 1.5σ .~~
- ~~107. — The method of claim 106, wherein the subject is enrolled in the clinical trial when (i) the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is below 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is below 1.8σ , or (iii) the ratio of tau phosphorylation at T181 to total tau and the~~

ratio of tau phosphorylation at T217 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is below 1.9σ .

~~108. — The method of claim 106, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau and the ratio of tau phosphorylation at T217 to total tau is above 2σ and tau phosphorylation at T205 is below 2σ .~~

~~109. — A method for enrolling a subject in a clinical trial, the method comprising — (a) providing an isolated tau sample obtained from the subject and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and — (b) enrolling the subject in a clinical trial when tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217 is about 1.5σ or above, where σ is the standard deviation defined by the normal distribution of tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.~~

~~110. — The method of claim 109, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T217 and T205 is above 1.5σ .~~

~~111. — The method of claim 110, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T217 and T205 is above 1.75σ , is above 1.8σ , or is above 1.9σ .~~

~~112. — The method of claim 110, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T217 and T205 is above 2σ .~~

~~113. — The method of claim 109, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181 and T205 is above 1.5σ .~~

- ~~114. — The method of claim 113, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181 and T205 is above 1.75σ , is above 1.8σ , or is above 1.9σ .~~
- ~~115. — The method of claim 113, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181 and T205 is above 2σ .~~
- ~~116. — The method of claim 109, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181, T205, and T217 is above 1.5σ .~~
- ~~117. — The method of claim 116, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181, T205, and T217 is above 1.75σ , is above 1.8σ , or is above 1.9σ .~~
- ~~118. — The method of claim 116, wherein the subject is enrolled in the clinical trial when tau phosphorylation at T181, T205, and T217 is above 2σ .~~
- ~~119. — A method for enrolling a subject in a clinical trial, the method comprising~~
~~—— (a) providing an isolated tau sample obtained from the subject and measuring total tau and measuring tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217; and~~
~~—— (b) enrolling the subject in a clinical trial when the ratio of tau phosphorylation at (i) T217 and T205, (ii) T181 and T205, or (iii) T181, T205 and T217 to total tau is about 1.5σ or above, where σ is the standard deviation defined by the normal distribution of total tau and tau phosphorylation at T217 and T205, T181 and T205, or T181, T205 and T217 measured in a control population without brain amyloid plaques as measured by PET imaging and/or A β 42/40 measurement in CSF.~~
- ~~120. — The method of claim 119, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T217 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is above 1.5σ .~~

- ~~121. — The method of claim 120, wherein the subject is enrolled in the clinical trial when (i) the ratio of tau phosphorylation at T217 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is above 1.75σ , (ii) the ratio of tau phosphorylation at T217 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is above 1.8σ , (iii) the ratio of tau phosphorylation at T217 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is above 1.9σ .~~
- ~~122. — The method of claim 120, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T217 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is above 2σ .~~
- ~~123. — The method of claim 119, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ and the ratio of tau phosphorylation at T205 to total tau is above 1.5σ .~~
- ~~124. — The method of claim 123, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau is above 1.75σ and the ratio of tau phosphorylation at T205 to total tau is above 1.75σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8σ and the ratio of tau phosphorylation at T205 to total tau is above 1.8σ , (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9σ and the ratio of tau phosphorylation at T205 to total tau is above 1.9σ .~~
- ~~125. — The method of claim 123, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau is above 2σ and the ratio of tau phosphorylation at T205 to total tau is above 2σ .~~
- ~~126. — The method of claim 119, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau is above 1.5σ , the ratio of tau phosphorylation at T205 to total tau is above 1.5σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.5σ .~~

- ~~127. — The method of claim 126, wherein the subject is enrolled in the clinical trial when (i) the ratio of tau phosphorylation at T181 to total tau is above 1.75 σ , the ratio of tau phosphorylation at T205 to total tau is above 1.75 σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.75 σ , (ii) the ratio of tau phosphorylation at T181 to total tau is above 1.8 σ , the ratio of tau phosphorylation at T205 to total tau is above 1.8 σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.8 σ , (iii) the ratio of tau phosphorylation at T181 to total tau is above 1.9 σ , the ratio of tau phosphorylation at T205 to total tau is above 1.9 σ , and the ratio of tau phosphorylation at T217 to total tau is above 1.9 σ .~~
- ~~128. — The method of claim 126, wherein the subject is enrolled in the clinical trial when the ratio of tau phosphorylation at T181 to total tau is above 2 σ , the ratio of tau phosphorylation at T205 to total tau is above 2 σ , and the ratio of tau phosphorylation at T217 to total tau is above 2 σ .~~
- ~~129. — A method as recited in any one of claims 89 to 128, wherein the subject is enrolled in the treatment arm of the clinical trial.~~
- ~~130. — A method of claim 129, wherein the treatment arm of the clinical trial comprises administering a pharmaceutical composition to the subject.~~
- ~~131. — A method as recited in any one of claims 49 to 89 or claim 122, wherein the pharmaceutical composition comprises an A β or tau therapy.~~
- ~~132. — The method of claim 131, wherein the A β or tau therapy is an amyloid beta targeting therapy, a kinase, a kinase inhibitor, or a phosphatase.~~
- ~~133. — A method as recited in any one of claims 1 to 132, wherein the subject has a gene mutation known to cause dominantly inherited Alzheimer's disease.~~
- ~~134. — A method as recited in any one of claims 1 to 132, wherein the subject does not have a gene mutation known to cause dominantly inherited Alzheimer's disease~~

~~135. — A method as recited in any one of claims 1 to 134, wherein the isolated tau sample comprises tau that has been purified from blood or CSF by affinity purification.~~

~~136. — The method of claim 135, wherein the isolated tau sample comprises tau that has been purified from blood or CSF by affinity purification using a ligand that specifically binds an epitope within the mid domain of tau, and optionally with a second ligand that specifically binds an epitope within the N-terminus of tau.~~

~~137. — A method as recited in any one of claims 1 to 135, wherein tau phosphorylation is measured by mass spectrometry.~~

1. An invention not claimed in any divisional application.